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## THE PRESENT ASPECT OF SOME VEXED QUESTIONS RELATING TO TUBERCULOSIS, WITH SUGGESTIONS FOR FUTURE RESEARCH WORK.*

By E. L. Trudeau, M. D., *Saranac Lake, N. Y.*

*Gentlemen:*—I venture to say a few words to you to-day on some of the vexed questions connected with the study of tuberculosis. Any of us who can look back some twelve or fifteen years can bear testimony to the progress which has been made by experimental research in our knowledge of this disease. Viewed in the light of the past it would seem that the future is full of promise as well as of unsolved problems. It is not, however, of the past triumphs of the experimental method that I wish to speak so much as of some of the as yet unanswered questions relating to tuberculosis which confront us at every step, and on which we so greatly need light before we can hope for larger results in staying the ravages of this widespread disease. I venture, also, to make a few suggestions as to what seem to me to be the most promising lines for future work in relation to the etiology, pathology, prophylaxis, bacteriology, diagnosis and treatment of tuberculosis.

### Etiology.

In regard to etiology, we need to know more as to the cause of the wide variations in the manifestations of the disease. Are these due to differences in the virulence of the infecting germ, to variations of the resisting power of the tissues, natural or acquired, or to both these factors?

What constitutes virulence in the infecting bacilli? Is it due to an increased capacity for elaborating toxins in greater quantity, or to the elaboration of more highly toxic products by the microbes, or does increased virulence depend merely on an inherent capacity of the germ to grow and spread more rapidly in the body?

In this connection I may state that, in my experience, tuberculin made from the culture fluid in which bacilli attenuated by long cultivation have grown is apparently as efficient in producing the usual tuberculin reaction in tuberculous men, and in killing tuberculous animals, as tuberculin derived from the most virulent cultures.

We need more light of an exact nature in regard to the various channels by which the bacillus gets access to the body, and in this connection it may be noted that the large proportion of cases presenting adenoid growths in the nasal fossæ which react to tuberculin would indicate that this portion of the respiratory tract is more frequently a channel of primary infection than is generally recognized.

*A Lecture delivered at the Johns Hopkins Hospital, on May 1, 1899.

What is predisposition? It may be individual or racial. Individual susceptibility may be inherited or acquired. It is, in either case, greatly influenced by all factors which tend to produce lowered vitality and imperfect nutrition, and which may be grouped under the terms heredity and environment. A susceptibility to the disease may be inherited; an unfavorable environment may precipitate infection, whereas a favorable one may avert it and even arrest and cure the disease when it has begun to develop. Racial susceptibility presents to the experimenter many curious problems for study which show that the line which divides immunity from susceptibility is a narrow one. Thus we find chickens highly susceptible to infection with the avian variety of the tubercle bacillus, while they resist inoculation with the bovine and especially the human bacillus. Indeed, so insusceptible are they to the human bacillus that they resist feeding for months on tuberculous sputum, and I have made repeated intra-peritoneal inoculations of large quantities of the most virulent cultures of human bacilli in a great number of chickens without the slightest deterioration in health resulting, and these birds when autopsied showed no trace of the injections or any evidence of disease in any organ. The guinea-pig, on the contrary, succumbs readily to inoculation with human bacilli, and is killed even more quickly by the bovine variety, but resists injections of avian cultures, which produce generally only a local ulceration in these little animals. The rabbit, on the other hand, is killed by all three varieties of the tubercle bacillus. Some slight artificially produced variations, however, may efface the resistance of the chicken to the human, and that of the guinea-pig to the avian bacillus. Nocard[1] has recently reported that by cultivating for some time human tubercle bacilli, enclosed in celloidin capsules within the peritoneal cavity of chickens, he could obtain cultures which not only grew well within the capsules when in the peritoneum of these birds, but had acquired the power of killing them when inoculated in the usual way. Although the guinea-pig resists infection with avian bacilli, Dr. Baldwin has noted at the Saranac Laboratory that this variety of the tubercle bacillus if passed through several rabbits, which it kills by intravenous injection in about twenty-five to thirty days, has become so altered that it has acquired virulence for the guinea-pig, and will then kill these little animals as well as the human bacillus does.

### Pathology.

Among the problems in pathology which require to be studied are:

(a.) The chemical changes in the quality of the digestive secretions, ptyalin, pepsin and trypsin, which in common with the infectious diseases occur in tuberculosis, and their immediate causes.

(b.) Further studies of the blood in tuberculosis. The cause of the anæmia in this disease; whether due to the effect of the toxins directly on the blood cells or the blood forming tissues, or indirectly on the nerve centers, and the nature of this process.

(c.) We also need light on the exact pathological changes which result in cure in peritoneal tuberculosis after laparotomy, and the mechanism by which tubercle bacilli (usually so resistant to the action of the tissues) are disposed of in the cure which follows this operative procedure. Does tubercle represent a defensive effort on the part of the organism, or is it a nidus which favors the multiplication and subsequent dissemination of the germs? What are the causes which lead occasionally to the entire disappearance of the bacilli before death in acute miliary tuberculosis from the tuberculous lesions of man and animals, and what evidence is there that we may interpret this disappearance as indicative of an acquired immunity?

(d.) What are the factors determining local immunity in the tuberculous? Is it true, as Koch pointed out, that the tuberculous individual is relatively immune to reinoculation with the virus (just as the syphilitic cannot be reinfected during the active progress of the disease)? How are we to harmonize this view with (i) local extension of the disease; (ii) extension of disease in other regions, *i. e.* development of laryngeal secondary to pulmonary tuberculosis?

(e.) Very divergent opinions are held by capable observers with regard to the meaning of the presence of tubercle bacilli in milk, semen, urine, etc. The majority are of the opinion that wherever they are present in the excretions there must be active tuberculosis in the excreting organs. On the other hand, a large number of cases are on record in which no such tuberculosis has been discovered; and the conclusion reached is that the actual excretion of bacilli by the kidneys, mammary glands, testes, etc., may occur. The question ought to be settled, *i. e.* by intravenous inoculations and observations upon the secretions at successive periods to determine (i) the earliest period at which the bacilli are discoverable in the secretions; (ii) the possible taking up of bacilli by endothelial and gland cells in the excretory glands; (iii) the difference, if any, in the appearance and properties of bacilli cast off by ulceration into the secretions and those truly excreted.

(f.) The production both within the body and outside of "beading" of the tubercle bacilli; its meaning; whether such beaded forms are degenerate or resistant forms (due to reaction of bacilli towards body fluids); relationship, if any, between beading and spore formation; what is the true nature of the tubercle bacillus? Is it a bacillus at all?

### Prophylaxis.

We need still further studies on the various sources of infection. Until recently we have looked upon the dried sputum of pulmonary tuberculosis, the dejections from the bowels of patients suffering from tuberculous enteritis, and the milk of tuberculous cows, as practically the only sources of infection to be guarded against. That the dried sputum is not the only source of danger has been shown by the recent work of Flügge,[2] who has demonstrated that the throat and mouth secretions of most tuberculous patients when atomized by the act of coughing may be a real source of infection to those about them. Some method of determining to what extent this source of danger exists, and which types of cases are most apt to thus spray bacilli about them in fine particles of saliva or throat mucous, would be of great value to preventive medicine.

Dr. Baldwin's[3] studies at the Saranac Laboratory have also shown that the hands of patients using handkerchiefs may, in the majority of cases, be the carriers of unsuspected bacilli.

Practical suggestions as to the education of the masses in regard to the sources of infection, and studies which will give us more light on the best and most practical methods to guard against them, would be of inestimable value. Under this head would be comprised practical suggestions as to the care of dust in living rooms, cars and public buildings, and better methods of the disinfection of these places by artificial means; as well as improved plans for ventilation and light in buildings, and the general dissemination among the masses of a better knowledge of personal hygiene.

A most promising prophylactic measure would be the establishment of state and municipal sanitaria in favorable localities for the treatment of incipient cases, and of special hospitals on the outskirts of large cities for the care of advanced and hopeless ones. It does not seem unreasonable to hope that a general adoption of this plan would in itself materially reduce the mortality from tuberculosis directly by curing a fair proportion of cases, and by the educating patients as to the care of their health, and indirectly by removing from crowded communities a large number of individuals who are a constant source of danger to those about them. More facts bearing on sanitaria, their location, construction, equipment and administration, would be of inestimable value.

The production of relative immunity by preventive inoculation belongs to the field of prophylaxis, and offers a most enticing subject of study; but I will refer to this more fully later on.

### BACTERIOLOGY.

Studies relating to artificial methods of exalting and attenuating the virulence of the tubercle bacillus are much needed, as they bear directly on the possibility of producing artificial immunity by preventive inoculation, and of obtaining an efficient antitoxic serum for the treatment of the active forms of the disease. Other bacilli, like the smegma bacillus and the bacillus of timothy-grass, which present nearly the same morphological appearances, the same peculiar reactions to staining methods as the tubercle bacillus; the bacteria which produce pseudo-tuberculosis, offer a most interesting field for further research.

Further light on tuberculin, the best methods of obtaining this toxin of standard strength, the influence of the virulence of the germs from which it is produced, and of the culture medium on which they grow, the technique of manufacture, etc., would be of great value. Dönitz[4] has recently shown that specimens of tuberculin obtained from different sources vary in strength as one in three.* In relation to this subject my own observations so far have tended to the belief that as efficient a tuberculin can be made from attenuated as from virulent cultures, but as the non-virulent cultures grow generally more luxuriantly it may be that they produce more toxin, though of less potency, while the virulent germs elaborate a more toxic product but less in quantity.

It is greatly to be desired that physiological chemistry shall separate the various substances elaborated by the bacilli or contained in their bodies, and that the toxicity of each of these shall be determined and their influence on the cell and the living animal studied. Researches in this direction have been begun by Drs. Levene and Baldwin at the Saranac Laboratory. Dr. Levene[5] has already found that "the body substance of tubercle bacilli does not contain any products of the albumin nature; that like the nuclei of cells it consists mostly of nucleoproteids; that one of the nucleoproteids differs from all the other nucleoproteids inasmuch as it is not precipitated by magnesium sulphate (and in this point resembles nucleohiston), and does not give the Biuret test; that it contains nuclein or nucleins as such." The three different proteid substances contained in the bodies of the tubercle bacillus have different coagulation points; the first from 50 to 64°C., the second from 72 to 75°C., the third from 94 to 95°C., the last being very rich in phosphorus. Dr. E. R. Baldwin is about to make some experiments bearing on the toxicology of these three proteids. As such large quantities of dried T. B.'s are necessary for each chemical and toxicological experiment the completion of the work necessarily will require some time. Researches on the chemistry of the tubercle bacillus have also been published recently by Ruppell,[6] working in Behring's laboratory, and by Jules Auclair,[7] from the laboratory of Professor Grancher.

A most promising field of research has recently been opened by the successful cultivation by Nocard of various microorganisms enclosed in celloidin capsules and inserted into the peritoneal cavities of living animals. These little celloidin cells allow to a limited extent the passage of some of the animal fluids into the capsule, thus affording a sufficient pabulum for the growth of the germ while protecting the microbes from the direct action of the body cells, and also permit the toxic substances elaborated by the bacteria to pass through and be taken up into the general circulation, while egress of the germs and their dissemination throughout the system of the animals is prevented. Experiments by these methods offer two very broad fields: the study of the influence of cultivation under such conditions upon the germs, their virulence and their products, and the study of the effect of freshly and continuously elaborated toxins on the living organism while the latter is protected from the direct pathogenic consequences of the spread of the microbe throughout the system at large. We may hope by this line of research to obtain more light on the mechanism of infectious diseases, and the reactions of the living tissues to the toxic products of the microbes, and it would seem to open new possibilities in attempts at the successful production of artificial immunity and the obtaining of antitoxic substances for the treatment of diseased conditions.

After prolonged cultivation by this method Vincent[8] succeeded in changing the harmless varieties of saprophytes into parasites, which gradually acquired the power of producing toxins, and ultimately of killing animals. Nocard[9] found, as

*As in the use of tuberculin for diagnosis the test is only a qualitative one, the practical importance of such variations is somewhat lessened.

already mentioned, that the human tubercle bacillus, which is non-pathogenic for fowls, after cultivation within these celloidin capsules which had been inserted into the peritoneal cavity of chickens, acquired after a time the power to kill these animals when inoculated in the peritoneum.

We need further knowledge on the relative pathogenic properties for man of the recognized varieties of the tubercle bacillus, the human, the bovine, and the avian.

### Diagnosis.

The value of any addition to our knowledge which will enable us to make a positive diagnosis at the earliest possible moment after infection has occurred must be conceded, for the chance of cure depends greatly on the early detection of the disease, and observations in the autopsy room have taught us how often nature can cure tuberculosis in its incipiency. We should in many cases no longer be content to wait for the appearance of expectoration containing bacilli, for marked physical signs, or for an unmistakable clinical picture. It seems to me we have in the tuberculin test a most delicate and searching means of detecting tuberculous disease when this cannot be done positively in any other way. We need more exact knowledge concerning the practical application of the tuberculin test in man, and we greatly need more light on the best method of applying this test, its exact value, its errors, their cause, and its possible dangers; in what other pathological conditions the reaction to tuberculin may occur; —and are the reactions which take place with considerable frequency in other diseased conditions due to them, or do they invariably indicate a concomitant and unsuspected tuberculous focus in some part of the body?

We need to know more as to the mechanism of the tuberculin reaction. The most generally accepted theory at present in regard to it is, briefly, that the small dose of tuberculin injected is a partly specific irritant both to tuberculous foci and to the susceptible organism in general. It produces intense hyperæmia of all tuberculous tissue in the body (local reaction), and as the result of this hyperæmia much toxin stored up in the tubercles themselves is thrown into the general circulation and produces fever and the characteristic symptoms which go to make up what is termed "a general reaction." That these poisons stored up in the tubercles are in part at least derived from the dead or weakened bacilli has been shown by the experiments of Babes and Proca,[9] who found that if two sets of rabbits be injected with equal quantities of living and dead bacilli the latter react to the tuberculin test at a much earlier period than those inoculated with living germs. This hypothesis that the general reaction is brought about by the toxins already stored up in the tuberculous lesions and exploded as it were by the hyperæmia produced about these lesions as a result of the test injection of tuberculin, is borne out by the fact that a greater amount of albumose can be recovered from the evaporated urine collected during the reaction than was contained in the test injection; also by clinical observations which indicate that patients suffering from localized surgical tuberculous processes of limited extent, and where the vascular supply to the part is limited, require a larger test injection to produce the reaction than those who have extensive or scattered visceral lesions in highly vascular organs like the lungs.

A very general impression seems to prevail that the tuberculin test is dangerous and tends to aggravate the disease. This impression had its origin, no doubt, in Virchow's statement that the autopsies which he made upon the first patients treated after Koch's method by repeated and increasing doses of tuberculin, so as to produce frequent and violent reactions, revealed in an unusual number of instances the presence of apparently new tuberculous foci at a distance from the original and recognized lesions. It may be conceded that violent and repeated reactions when brought about in patients suffering from extensive visceral disease tend to exhaust the already overtaxed defensive resources of the organism, and may in this way aggravate the disease. But the conditions are very different in incipient cases where the resistance of the patient is as yet but little impaired, and where it is necessary to produce only one moderate reaction. Even if the correctness of Virchow's observations be conceded, the finding of more pronounced and distant lesions may not necessarily mean that the bacilli were disseminated through the system as a result of the tuberculin treatment. We have ample clinical and experimental evidence that the local reaction resulting from an injection of tuberculin makes apparent the presence of latent and unsuspected tuberculous lesions, but no proof has been brought forward to show that the bacilli are scattered through the system or that new foci are produced as a result of such injections.

In a recent study by A. Broden[10] on the Treatment of Experimental Tuberculosis of the Peritoneum in Dogs by Tuberculin Injections, he points out that the extent and number of tubercles visible in the peritoneum when the treated animals are killed at an early stage of the disease are greatly in excess of that noted at the same stage in the controls. On careful microscopical study, however, these large and more numerous tubercles are found to consist of an aggregation of leucocytes, which appear to represent a defensive effort on the part of the system to limit the disease, as the bacilli in them are seen to be very few in number, beaded, and soon entirely disappear, leaving only slight fibrous lesions from which the animal ultimately completely recovers. In the controls killed at the same period the macroscopical appearances show but little evidence of disease, but a microscopical study of the peritoneum reveals everywhere small nodules swarming with large numbers of short, well-stained bacilli, the disease going on rapidly to a fatal termination.

In my experience no injury to the patient has occurred thus far as a result of a test injection of tuberculin where small graded doses at two or three intervals have been used for diagnostic purposes, and all of the hospital physicians with whom I have conversed, who have practiced this method, have apparently had a similar experience, and none, to my knowledge, has abandoned it on account of any evidence of injury to the patient. If we consider the overwhelming importance of this subject in our struggle against tuberculosis, it is greatly to be hoped that a thorough study of the method will bring to light the true facts as to its exact value, and its limitations and possible objections.

The application of X-rays to the diagnosis of incipient pulmonary tuberculosis promises to be of practical assistance, as the height of the excursion of the diaphragm and the appearance of a slight shadow over the suspected area in the lung, when considered together with the rational symptoms and any trifling deviation from the normal sounds in the lung, enable the physician to reach a positive conclusion in many cases before the appearance of expectoration containing bacilli, or the unmistakable symptoms of the disease are present. A case I saw recently with Dr. Francis Williams, of Boston, illustrates the corroborative value of an X-ray examination in early and doubtful cases, and that by a combination of the usual clinical methods with a thorough X-ray examination, a positive conclusion as to the presence or absence of the disease may often be reached before cough and expectoration are present, or any appreciable deterioration of the general health has occurred. I had suspected the presence of tuberculosis in a hospital patient of Dr. Williams' merely because the temperature chart showed a rise of one-half to one degree occasionally in the evening, and because I thought I could detect very slight evidence of consolidation at one apex. These were all the symptoms present. Under the X-ray the case showed that the diaphragm on the suspected side was higher than the normal, and its excursion appreciably diminished on that side, while a slight shadow could be made out at the apex. I suggested the tuberculin test, and the patient had a typical reaction, the temperature reaching 102.5, fourteen hours after the injection.

### TREATMENT.

The climatic and open-air treatment of tuberculosis in especially constructed sanitaria is at present conceded to offer the patient the best chance of recovery, but this needs elaboration, and studies which would afford more exact indications for such class of cases as to the proper application of rest or exercise, exposure to the air, feeding, hydrotherapy; the use of tonics and reconstructives, and the regulation of the smallest details of the daily life, would be of great value.

The obtaining of a serum that would be antitoxic for the infections concurrent with tuberculosis would make us much less hopeless in the presence of such cases, while at present we must be contented to rely on fresh air, rest, food and alcohol to relieve this desperate condition.

To laboratory researches we may yet look for some general specific method of treatment, either by preventive inoculation or the production of an efficient antitoxic serum for tuberculosis. It is true that, in spite of the claims so constantly made, little of practical value to the tuberculous patient has been accomplished so far by the enormous amount of research work bearing on attempts to produce immunity in animals against tuberculosis and to obtain an efficient antitoxic serum for the poison of this disease.

To many minds there seems no reason to hope that any efforts tending to the production of artificial immunity in this disease will ever be successful, and it is true that little can be found in the clinical history of tuberculosis which would lead us to believe that such an immunity ever occurs in the natural course of the disease, as recovery from a tuberculous manifestation in any part of the body does not seem to afford any protection against a subsequent and often fatal outbreak of the malady. It would be presumptuous, however, in view of the recent advances made in this direction in other infectious diseases, to deny absolutely the possibility of solving this problem, and some experimental evidence is accumulating of late which tends to prove that the resistance of the body to a virulent tuberculous infection can be greatly increased by preventive inoculation.

I will not here review the work done in this direction by Richet, Héricourt, Grancher, Martin and others, as it is no doubt familiar to you, but I will occupy your time by referring, more particularly to my own experience in this direction, not on account of the practical value of the results I have obtained, but because my observations having been made entirely independently seem to add some confirmatory evidence to the partial success already attained by others in this field. In common with many other experimenters, I failed to obtain any appreciable results by preventive inoculations of the various products to be found in liquid cultures or by the inoculation of the bodies of dead tubercle bacilli. I was driven, therefore, to attempt to reach the end in view by making use of the living germs themselves, attenuated by various methods.

The first evidence of any protection which I succeeded in obtaining was in 1893, which I detailed in a paper read before the Association of American Physicians in May, 1894. I found that by subcutaneous preventive inoculations of attenuated living cultures of avian tubercle bacilli I was able to increase the resistance of the rabbit to infection with virulent living mammalian culture. The photographs which I show you demonstrate the degree of immunity obtained. The test inoculations were made in the eye, where the immediate result could best be studied and controlled. The eyes of the controls were gradually destroyed by the progressive tuberculous process, while those of the vaccinated animals, after undergoing a certain inflammatory reaction, returned more or less completely to their normal condition. Unfortunately, many of the animals died of the attempt at vaccination, and complete immunity was manifested only in a few; while in others, similarly treated, the eyes were eventually either partially or totally destroyed. I have also obtained a marked degree of success in protecting guinea-pigs by cultures of mammalian bacilli attenuated simply by prolonged growth on artificial media.

Dr. de Schweinitz[11] was the first to call attention to his results in protecting guinea-pigs by means of living attenuated cultures, and although my results have not thus far been as good as his, my experience in the past four years shows that a very marked degree of increased resistance to tuberculous infection can be induced in these animals, as well as in rabbits, by such preventive inoculation. It is of interest to note that the culture used by Dr. de Schweinitz in his experiments was originally obtained by him from me, and is the same with which my own experiments were made. This culture originated from plants made on serum by me from the lesions of a rabbit infected with human tuberculosis in 1891, and has been grown on various media, principally on the ordinary

glycerin peptone bouillon, either neutral or slightly acid, ever since. I began to notice, after two years' cultivation, that a great majority of the guinea-pigs inoculated with this culture lived for many months beyond the usual time, and the virulence of the germ was evidently decreasing. It was not, however, until 1894 that I observed that many of these animals apparently recovered completely from the inoculation, while a few still died of chronic tuberculous lesions. At present, if twenty animals be inoculated with this attenuated germ, which has been grown for six years continuously on artificial media, with perhaps one or two exceptions, all survive for many months. It has been necessary, however, to keep the pigs for a long time, for occasionally some of them die of chronic tuberculosis even two and a half years after the attenuated inoculation.

What the attenuation of the bacillus is due to is still a matter of doubt in my mind. De Schweinitz is of the opinion that the acid in the media greatly hastens the attenuation, and has therefore grown his cultures on very acid media; but the germ undoubtedly loses its virulence if the cultivation is sufficiently prolonged, no matter what the media may be. I have varied the acidity of the media, but as yet have come to no definite conclusion on this point. In favor of Dr. de Schweinitz's view it may be stated that the tubercle bacillus loses its virulence much more rapidly while growing on potato which is slightly acid, than on serum, but these two media differ also in many other respects besides in reaction.

It is a well-known fact that any living organism loses any attribute which through many generations its environment does not call into use. While living a saprophytic existence the tubercle bacillus has no need for the exercise of that characteristic which is known as its "virulence" and which means the power to cope successfully with the resisting elements of living tissues, and it may be that this attribute is lost to it by its disuse through the millions of generations the germ passes through while growing for so long on artificial media. However that may be, it is certain that the tubercle bacillus is robbed of its virulence with the utmost difficulty. All other methods of attenuation hitherto employed—heat, time, antiseptics, etc.—aim a blow at the viability of the germs sought to be attenuated, but do not alter their biological characteristics. They are either killed, in which case they produce no disease, or else they survive sufficiently to grow in the body and ultimately destroy the life of the animal. Prolonged cultivation, on the other hand, gives us a culture which grows vigorously, but which has lost to a great extent its specific pathogenic powers.

A certain disturbance of health and loss of weight are always caused by the inoculation of this attenuated culture, but the animals after three months seem to have completely recovered. If at this time they are inoculated with virulent bacilli, together with an equal number of controls, the prolongation of life in the vaccinated animals will be apparent in every case. In several lots I have noticed the death of all the controls to occur before a single vaccinated animal had died. Complete immunity, however, has not been attained in my experience so far by this method, although some of the animals have occasionally lived as long as eighteen months after the virulent inoculation.

I will not weary you with any of the details of these experiments, which are still incomplete, but merely report the gross results which I have obtained thus far in work done on a total of one hundred and twenty-two guinea-pigs. In 36 controls the average life was 57.2 days, and in the 66 vaccinated animals it was 154.3 days, so that the vaccinated animals lived nearly three times as long as the controls. Some of the pigs survived the virulent inoculation as long as eighteen months. This includes all the experiments on guinea-pigs, some of which were made before the germ was very much attenuated. Intravenous inoculation of this attenuated culture protects rabbits to about the same extent, but in them, as in the guinea-pigs, the immunity is relative except in a few cases where the protection seems to be almost complete.

It would seem at first sight that the evidence brought forth by these experiments tends to prove positively that at least relative artificial immunity had been produced in these animals. The evidence is incomplete, however, in so far as it relates to the complete recovery of the animals from the protective inoculation. I have kept vaccinated pigs which lived nearly three years in apparently good condition and yet ultimately died of chronic tuberculosis. It is possible, therefore, that these experiments only prove that the disease is not auto-inoculable, and that an animal in which a very chronic form of tuberculosis has been induced artificially is not susceptible to reinoculation with a more virulent infecting material. This, I believe, is true of syphilis, a disease which closely resembles tuberculosis in its course and various manifestations.

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# INFUSION OF SALT SOLUTION COMBINED WITH A SPECIAL METHOD FOR THE ADMINISTRATION OF OXYGEN INHALATIONS AS A TREATMENT IN PNEUMONIA.*

BY CLEMENT A. PENROSE, M. D.

It has been the custom in the Johns Hopkins Hospital for several years to use infusions of normal salt solution (.6%) in cases of collapse, especially during or after severe surgical operations. In such cases the pulse is generally the index to the necessity for infusion or the amount infused.

During my gynæcological service in this Hospital I had the opportunity of observing the effects of infusions in a number of such cases, and was much impressed by the fact that in many the stimulation to the respiration was more marked than to the heart. This was true especially of those cases who, taking the anæsthetic badly, were in a more or less state of asphyxia.

The possibility of this respiratory effect being in addition to others of great benefit in conditions like pneumonia occurred to me then, but it was not until I had entered the service of Dr. Osler that the opportunity arose to demonstrate the truth of such speculations. He kindly permitted me, February 14, 1898, to try the effect of salt infusions as a last extremity in a very grave case of pneumonia, to whom later inhalations of oxygen were administered after a special manner. Since then the same treatment was used by me in two other cases of pneumonia; one, on the surgical side following an operation, and the other in private practice.

The infusions of salt solution were given in the usual fashion employed in the Hospital, *i. e.* the salt solution, at a little above body temperature, is poured into a graduated bottle, from the bottom of which runs a long rubber tube. The needles, which are introduced under the breast, or into the subcutaneous tissues of the thighs, etc., are connected with this tube. The pressure is regulated by elevating the bottle or by means of a rubber bulb, with valves, which is attached to the stopper of the bottle, and thus air can be forced into the space above the salt solution. At intervals a careful examination of the heart is made, especial attention being paid to the second pulmonic sound, with instruments in readiness for instant bleeding if this become too accentuated or murmurish in quality. Inhalations of oxygen in connection with infusion are given according to a special method, which is as follows:—in place of the delivery nozzle usually adopted, a glass funnel is substituted, which is held by a framework resting on the bed about two inches from the face, and supplies oxygen to both mouth and nostrils without interfering in any way with the breathing. The oxygen is passed through a wash bottle containing a pint of hot water in which has been placed one dram of an inhalation mixture, the formula of which is:—

℞

| | | |
|---|---|---|
| Creosoti (beechwood), . . | ℥ ss | (one-half ounce.) |
| Olei Terebinthinæ, . . . | ℥ ss | (one-half ounce.) |
| Tr. Benzoini Comp. . . . | ℥ ii | (two ounces.) |

The inhalations are given at intervals whenever lips or finger tips become bluish, are continued till the color is normal, usually from ten to fifteen minutes in those who give a good reaction.

The first two cases of pneumonia on which I have tried infusions of salt solution combined with this special method of giving oxygen inhalations died, the last case made a perfect recovery. It should be remembered, however, that all these cases were considered hopeless, and had received the usual treatment for pneumonia before this method was resorted to. Since I left the Hospital, September 15, 1898, this treatment has been resorted to in several other severe cases, and also by physicians in the city in their practice, with most gratifying success. In the two cases that died, the prolongation of life and the relief of symptoms, etc., were so marked that I regretted this treatment had not been employed earlier. From the brief histories which are presented, it will be seen that all three cases represented the severest types of pneumonia with every reason for unfavorable prognoses.

CASE I, J. O., admitted to Ward F (medical) February 12, 1898, on the 5th day of the disease. The patient was an ill-nourished, feeble man of fifty-two years, with a bad alcoholic history, complete consolidation of the right lung, a temperature ranging from 104° to 105.5°, and a muttering delirium, with twitching of the muscles, who in addition had chronic Bright's disease, with almost anuria for two days after admission. The pulse was very weak and wavering, 104 per minute, respiration shallow, labored and ranged about 40 per minute. Dr. Osler saw the patient two days after admission, the day upon which infusions were begun, and said the man was moribund, and would probably not live till night. The results of infusion were most surprising. On the first day, after 2700 cc. salt solution had been infused, the following was noted:—"the pulse became full and regular; the rate however remained about 104, respirations became deeper and fell to 28 per minute." On the second day 4000 cc. more of salt solution were infused. The patient became conscious after three days of muttering delirium, and voided large quantities of urine. The pulse and respirations remained about the same. On the third day 3000 cc. salt solution were used with little effect. The pulse was 112, and respirations 44 per minute.

On the fourth day of treatment 3000 cc. of salt solution were infused. The temperature fell to 100.4°, and the patient had a profuse perspiration. A crisis seemed imminent. Later however the pulse ran up to 140, and respirations to 52, and as considerable cyanosis developed, inhalations of oxygen were given according to the special method mentioned above. Almost immediately the patient's lips and nails became a brilliant red. He went to sleep, and the tongue and mouth were noted to be much less foul. The pulse remained about the same, but respirations fell from 56 to 52 per minute, and

* Read before the Medical Society of the Johns Hopkins Hospital, Monday, January 23, 1899.

became less labored. Oxygen was afterwards given at intervals with great comfort to the patient, the inhalation mixtures seeming to have an expectorant action, as the sputum became less tenacious and more watery, due, no doubt, in part to the salt infusion.

On the fifth day (twelfth day of the disease), patient began to fail and required 6000 cc. of salt solution throughout the day, with almost a constant supply of oxygen. The pulse was 140 and very irregular; respirations were 56, and shallow. About noon I bled the patient from the arm and removed thirteen ounces of a dark, quickly clotting blood. This was done because the second pulmonic heart sound became distinctly murmurish. The pulse fell after the bleeding from 140 to 132, respirations from 56 to 32, and again, a good reaction to oxygen was given. The patient lived all day in a semi-conscious condition, but at 9.30 P. M., died very quietly in spite of all further efforts.

The leucocytes in this case fell from 16,000 the day infusions were begun, to 9200 the day of death.

Case II, Dr. B., admitted June 26, 1898, Ward C (surgical side). The patient was a large, stout man aged fifty-two years; good family history; operated on July 11, for carcinoma of the tongue; right half of tongue removed, with glands of neck, etc. The anæsthetic used was chloroform. Pneumonia followed the operation on the sixth day, due to aspiration of food. It was patchy in character, and scattered throughout both lungs.

On the second day after the development of pneumonia, the patient's condition became so desperate that salt infusion combined with inhalation of oxygen was begun. In this case the same good effects were noted as in the former. In addition, the wound in the neck which, with the half of tongue remaining, had become very foul and offensive, in a few hours became quite clean and sweet. The patient died on the fourth day of the pneumonia, having received 13,000 cc. of salt solution in all. He showed, though in a very low condition, marked reaction to oxygen after being infused.

Up to this time little had been accomplished as far as mortality was concerned, but in one case, I was contending with age and alcoholic history, and Bright's disease, and in the other with an aspiration pneumonia following a severe surgical operation; in both cases the treatment was employed late in the condition and as a last extremity. Recently I have had a case in private practice where the conditions with the exception of age seemed even more hopeless than in the other two, but which has made a remarkable recovery and fully compensates for the disappointment of losing the other two patients after they had shown such evident improvement.

Case III, Mrs. R., aged 34, married. Delicate constitution; had a slight cold for two to three days, in all probability, an attack of grippe, which was then epidemic. December 16, 1898, while standing before an open window, she felt a stabbing pain in the left side, which increased in severity. She went to bed and sent for the family physician. Her temperature rose steadily, and on December 19, four days later, reached 104°. The patient then became delirious and had, according to her physician, decided flatness throughout the upper left chest. The pulse was weak and thready; respirations rapid and shallow. The delirium in spite of treatment persisted, and the patient became progressively weaker. I was called in, in consultation, upon December 26, at 10 A. M. Her temperature was then 105.5°, her pulse irregular, 120 and over, very soft and weak, running in character. Respirations varying from 48 to 52 per minute were very shallow and labored; lips and finger tips much cyanosed. The patient was in muttering delirium, with marked twitching of the muscles, especially those of the extremities. The muscles of the neck were somewhat stiff. Her condition was so desperate that a thorough examination was out of the question. However, numerous crackling râles were heard throughout both chests and in the left upper front, the breath sounds had a decidedly tubular character. The back was not examined. 1000 cc. of normal salt solution were immediately infused in the right breast, and inhalations of oxygen were begun by my method, with immediate benefit. Respirations fell to 32 per minute and the twitching of the limbs grew less and the patient regained a normal color in a few minutes. The pulse showed some improvement in volume and tension, but the rate remained still about 120. Inhalations and repeated cold sponges were given all day at intervals, but with little improvement. The temperature fell a degree or so, but the meningeal symptoms became much more marked. At eleven P. M. severe convulsions set in, almost eclampsic in nature, and succeeding one another every three to four minutes. The patient was very blue. 2000 cc. more of salt solution were infused, and eight ounces of blood were removed from the left arm as the second pulmonic sounds had become murmurish. The blood was very dark and clotted immediately on standing. There was now decided improvement; the respirations fell from 48 to 24 per minute (just one half), and the oxygen which had apparently been of little service all day, in a short time gave a good reaction. The lips and nails became a good color; respirations steadily grew deeper and less labored. The tongue and mouth became cleaner and more moist, the pulse steadier and fell to 104 per minute. The convulsions gradually disappeared.

*December* 27, 4.30 P. M. The patient is much better, is conscious after *eight days* of muttering delirium. The temperature is 105.5°. She takes nutrition well, has voided much urine, and perspired freely. 600 cc. more salt solution were infused, and the rectum was irrigated with large quantities of this solution also. Oxygen was given at intervals to the patient more for her comfort than because of cyanosis. Mouth and tongue continued moist and clean; the breath was sweet, with a strong odor of the inhalation mixture.

*December* 28. Temperature 102°; general condition much better; pulse is full and strong, regular and 117 per minute; respiration only 30, quiet; oxygen is now discontinued. From this time on the patient steadily improved; the temperature fell gradually by lysis, and on January 14, was normal. She has now fully recovered, has gone to the country, and has already gained several pounds. I consider this a remarkable case, a veritable resurrection, and which fully repays one for the time spent in vain on others. With such a high temperature, with muttering delirium for eight days and later convulsions, with grippe as a precursor to the pneumonia, in a naturally delicate woman, I am sure all will agree that the

prognosis was more than bad. The blood in this case was negative for the Widal typhoid test, the urine showed a considerable number of pus cells from a leucorrhœa, but no casts, etc.

In conclusion, I claim that the infusion of salt solution in pneumonia is a decided advance in its treatment if used by those familiar with the significance of the second pulmonic heart sound, and who are prepared to bleed immediately if this indicates danger. In my opinion, infusion, which is slower, is preferable to transfusion. It dilutes the toxines in the blood, relieving delirium, etc., and promotes their elimination through the sweat glands and kidneys. It lowers the temperature. It stimulates the heart. It lowers the rate of respirations and renders the breathing less labored. It seems undoubtedly to *render the patient more susceptible* to the influence of oxygen.

The use of a funnel in the administration of oxygen held by a framework has these advantages:

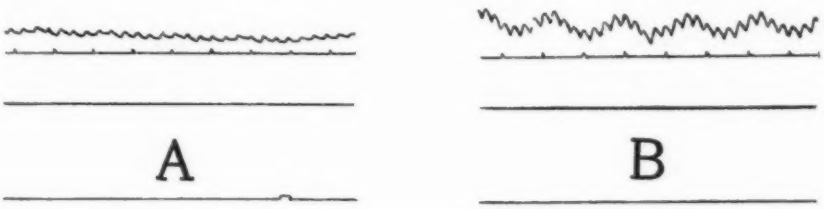
The patient gets oxygen through both the nostrils and mouth. There is no impediment to expiration, as is the case with a nozzle in the nose or mouth. The patient may go to sleep and still take the oxygen, which they frequently do, whereas the nozzle being uncomfortable and producing a blast, is apt to keep them awake. The passage of the oxygen through a hot inhalation mixture is more beneficial than when used alone. The vapors from such a mixture carried over with the oxygen certainly render the tongue and mouth less foul, the breath sweet, and promote expectoration,—and who can say it does not have some antiseptic effect on the lungs?

Oxygen alone being odorless, a patient if conscious will make greater efforts to breathe something which is tangible, and will not turn the head away, etc.

That cases which have been previously infused with salt solution react much better to oxygen has certainly been my experience. I have tried oxygen alone in several cases of pneumonia, and have the notes of the same with me, but not one, although representing pneumonias of a much less severe type, gave the remarkably quick reaction noted in the three cases where infusions of salt solution had been previously given. Oxygen, it is known, is held in the blood in two ways:—as a chemical compound with hæmoglobin and in solution; increasing the bulk of blood may increase its oxygen-carrying capacity as a whole, although diminishing it relatively; hence the advantage of supplying more oxygen.

Dr. Reid Hunt, of the Johns Hopkins University, has kindly told me of some experiments which he has made in the Biological Department on the effect of intravenous injections of saline solution into dogs. He finds that in curarized dogs in which artificial respiration is maintained, the injection of normal saline solution, or of Ringer's solution, will cause a marked increase in the amplitude of the respiratory undulations of the blood pressure. This change often occurs before there is any rise of blood pressure or appreciable change in the pulse rate. He thinks it is due to a larger volume of blood passing through the pulmonary vessels. The accompanying kymograph curves are taken from one of his experiments. A is a portion of the record before; B, after the injection of 700 cc. of warm Ringer's solution into the saphenous vein of a curarized dog.

In this, we would have then an experimental proof of my clinical observation, viz., that infusion of salt solution increases the circulation in the lungs, and therefore their ability to take up more oxygen. The oxygen capacity being increased as a whole by increasing the bulk of blood, gives us an additional factor.




## A NOTE ON THE PIGMENT PRODUCTION OF BACILLUS PYOCYANEUS AND BACILLUS FLUORESCENS LIQUEFACIENS.

BY PAUL GERHARDT WOOLLEY, B. S.

(*From the Pathological Laboratory of the Johns Hopkins University and Hospital.*)

Some time ago while studying cultures of B. pyocyaneus and B. fluorescens liquefaciens, the similarity of the pigments produced by these two organisms seemed to me to indicate a possibility of interchangeability of chromogenic function. In these two particular cases the chromogenic peculiarities on agar-agar of the B. pyocyaneus seemed to be more nearly like those of B. fluorescens, while chloroform solutions of the pigment from agar-agar cultures of B. fluorescens showed a faint trace of blue.

Babes, Fordos, Gessard and Kuntz showed long ago that B. pyocyaneus produced three pigments, one fluorescent, not soluble in chloroform, one blue, soluble in chloroform, and the other a red, pyoxanthin, supposed by Gessard to be an oxide of pyocyamin or the blue pigment.

Since these observations Gessard, Wasserzug and others have shown how easily achromatic and monochromatic varieties or "races" could be produced artificially.

What I intended to do was to place B. fluorescens lique-

faciens, which is the fluorescent bacillus most nearly akin to B. pyocyaneus in cultural and microscopic characteristics, under conditions most favorable for production of pyocyamin and see whether or not a "race" could be obtained which would produce pyocyamin. For this purpose I used the medium known as *Gessard's Agar*, which is a neutral mixture of agar-agar, peptone and glycerine, and which Gessard found to be the best medium for forcing B. pyocyaneus to a maximum production of its blue pigment with a minimum of the other two pigments. In these experiments I used samples of B. pyocyaneus obtained from six different sources, and samples of B. fluorescens from five sources. These were grown at room and blood temperature. Each culture made was allowed to grow for three days and then cultures were made on fresh media from the cultures already grown. In this way an uninterrupted series of cultures was made from each specimen of the organisms, and extending over twelve transplantations.

The result however was negative. For one or two generations two of the fluorescent varieties did give some blue pigment soluble in chloroform, but at the end of the series all of the cultures of B. fluorescens were colorless, and only one of the cultures of B. pyocyaneus was typical. That one was a specimen for which I thank Dr. Jordan, of the University of Chicago. Evidently the color-line is not to be crossed.

Besides these results, I was able to confirm the statements made by Gessard, Noesske and others that the absence of phosphoric acid in some form inhibits the production of fluorescence. I also am able to state that the magnesium in Uschinsky's fluid can be replaced by aluminum with no effect upon pigment production.

# EXPERIMENTS MADE TO DETERMINE THE EFFECTS OF SUGAR UPON THE PIGMENT FORMATION OF SOME OF THE CHROMOGENIC BACTERIA.

By Paul Gerhardt Woolley, B. S.

(*From the Pathological Laboratory of The Johns Hopkins University and Hospital.*)

Uniformity in the composition of culture media is one of the requisites of uniformity of observation in the study of bacteria in cultures. This is evident on its face; and yet it is probable that in the study of the bacteria in laboratory media the fact that a certain amount of sugar is present is not sufficiently considered, in spite of the fact that, in some conditions, for instance in the production of toxins by the B. diphtheriæ, the presence of sugar makes a great deal of difference. Of course the quantity of sugar in the ordinary bouillon media is very small, but it is large enough to allow B. coli communis some exercise of its fermenting functions, and is therefore appreciable, and may also make appreciable differences in results in observations. It was in view of such facts as these that I set out at Dr. Flexner's suggestion to make a series of experiments with sugar-free and sugar-containing media to see what the effects of sugar upon certain functions of certain bacteria might be.

For these experiments the chromogenic bacteria seemed to be best suited, one reason being that many of them are known to be prevented from producing their pigment in the presence of sugar, and this, if true, would make it easy to determine with greater or less certainty the relation between the chromogenic powers of the organisms and the sugar present in the medium.

As examples of the chromogens, I selected B. pyocyaneus, B. fluorescens liquefaciens, B. janthinus and B. prodigiosus. As examples of the sugars I used glucose, lactose and saccharose.

In order to have a sugar-free medium as a means of making "check" observations, I treated bouillon made from fresh beef, by the method of Theobald Smith, the essential of which is the destruction of the sugar, present in such an extract, by the help of B. coli communis. To this bouillon when rendered neutral and prepared in the usual way were added definite quantities of the three sugars. For the purposes of the experiments I used a 1 per cent. and a 2 per cent. solution of each of the three sugars. In all the experiments cultures were made in the sugar-free medium as "checks" upon the sugar-containing cultures.

In the first series of cultures, which were merely preliminary, the organisms were allowed to grow at a temperature of 37° C. until a maximum of pigment was developed. This time varied from seven to fourteen days. At the end of this time the cultures were sterilized and tested for sugar at leisure. Speaking generally, the results were that the pigment developed sooner in sugar-free bouillon and appeared earlier in the 1 per cent. sugar media than in the 2 per cent. media. The growth in itself was more rapid and luxuriant in the sugar-containing media, and at the end of the period of growth no sugar could be appreciated by Fehling's solution in glucose and lactose cultures, but some reduction did take place after inversion in saccharose cultures.

In the second set of cultures the same materials and the same organisms were used, but a temperature of 25° C. was adopted as a temperature best suited to B. pyocyaneus and B. prodigiosus at the same time. The cultures were allowed to grow not longer than seventy-two hours. One set was sterilized at the end of twenty-four hours, one at the end of forty-eight hours and one at the end of seventy-two hours. The results were as follows:

(In the following tables an × represents the smallest amount of color in growth present in the three cultures on the same line. A zero means total absence of color. An "S" in a subdivision of a column means that in testing with Fehling solution after sterilization, sugar was present. A zero in a like place means absence of sugar.)

CULTURES STERILIZED AT THE END OF 24 HOURS.

| Organism. | | Plain. | Glucose, 1%. | | Glucose, 2%. | |
|---|---|---|---|---|---|---|
| B. pyocyaneus | Pigment. | × × | × | | 0 | |
| | Reaction. | alk. | acid | S | acid | S |
| | Growth. | × | × × | | × × × | |
| B. prodigiosus | Pigment. | 0 | 0 | | 0 | |
| | Reaction. | alk. | acid | S | acid | S |
| | Growth. | × | × × | | × × | |
| B. janthinus | Pigment. | 0 | 0 | | 0 | |
| | Reaction. | alk. | acid | S | acid | S |
| | Growth. | × | × × | | × | |
| B. fluorescens | Pigment. | 0 | 0 | | 0 | |
| | Reaction. | alk. | acid | S | acid | S |
| | Growth. | × | × | | × × | |

CULTURES STERILIZED AT THE END OF 48 HOURS.

| Organism. | | Plain. | Glucose, 1%. | | Glucose, 2%. | |
|---|---|---|---|---|---|---|
| B. pyocyaneus | Pigment. | × × | × | | 0 | |
| | Reaction. | alk. | alk. | S | alk. | S |
| | Growth. | × | × × | | × × | |
| B prodigiosus | Pigment. | 0 | 0 | | 0 | |
| | Reaction. | alk. | ac. | 0 | ac. | S |
| | Growth. | × | × × | | × × | |
| B. janthinus | Pigment. | 0 | 0 | | 0 | |
| | Reaction. | alk. | ac. | S | ac. | S |
| | Growth. | × | × × | | × | |
| B. fluorescens | Pigment. | 0 | 0 | | 0 | |
| | Reaction. | alk. | alk. | S | acid | S |
| | Growth. | × × | × × | | × × × | |

CULTURES STERILIZED AT THE END OF 72 HOURS.

| Organism. | | Plain. | Glucose, 1%. | | Glucose, 2%. | |
|---|---|---|---|---|---|---|
| B. pyocyaneus | Pigment. | × × | × | | × | |
| | Reaction. | alk. | alk. | 0 | alk. | 0 |
| | Growth. | × | × × | | × × | |
| B. prodigiosus | Pigment. | × × × | × | | × | |
| | Reaction. | alk. | alk. | 0 | alk. | 0 |
| | Growth. | × | × | | × | |
| B. janthinus | Pigment. | × | × × | | × × × | |
| | Reaction. | alk. | alk. | 0 | alk. | 0 |
| | Growth. | × | × | | × | |
| B. fluorescens | Pigment. | × × | × | | × × | |
| | Reaction. | alk. | alk. | 0 | alk. | 0 |
| | Growth. | × | × | | × | |

(In these tables it will be noticed that glucose media alone were noted because it was impossible to make differential tests for the various products of decomposition of the complex sugars in the presence of each other, and so to give reliable results.)

From the above tables the following conclusions can be drawn: 1. That pigment is produced more readily in sugar-free media. 2. That growth is more luxuriant in sugar-containing media. 3. That pigment is produced earlier in 1 per cent. glucose media than in 2 per cent. media.

Cultures in media containing lactose and saccharose as well as those containing glucose give evidence that glucose offers the best nutritive advantages, that lactose is less readily used, and that saccharose is only with difficulty made use of by all of the bacilli with the exception of B. prodigiosus which seems to thrive equally well in all.

# CHRONIC MALARIAL NEPHRITIS, WITH REPORT OF A CASE.

BY CHARLES W. LARNED, M. D.

(*Assistant Physician to the Dispensary, The Johns Hopkins Hospital.*)

The two points of greatest interest in the case I have to report are, (1) the fact that the infection was of the quartan type, the rarest of the three recognized forms of malarial fever, having been noted in but about 8 per cent. of cases recorded in this institution, and (2) the associated nephritis which was almost certainly dependent upon this or a previous malarial infection. The only other possible predisposing cause was to be sought in an attack of measles during April, 1898. This however can be ruled out, since the attending physician states that the attack was light, and that there were no symptoms whatever suggesting involvement of the kidneys, and especially when we take into consideration the infrequency of measles compared with malarial fever in this locality as an etiological factor in nephritis.

As to the connection between measles and a consequent nephritis, the following citations are of interest: Tirard[1] says, "It is comparatively rare for albuminuria to be associated with measles, and there is reason for suspecting that some of the cases which have been described under this heading were really cases of scarlatinal nephritis." Blum[2] in a collection of 45 cases of measles records but one that showed any renal involvement. Carr[3] collected at the Infants' and Children's Hospital, Randall's Island, 107 cases of measles, only one of which showed a nephritis, the condition being associated also with broncho-pneumonia with purulent infiltration, emphysema and pleurisy. Albutt[4] in London, where malarial fever is so uncommon, has collected 136 cases of nephritis due to all causes; of these, he attributes 3 to measles and one to malarial fever and exposure. Smith,[5] Goodhart,[6] Ashby and Wright,[7] Tyson,[8] Osler,[9] Anders,[10] and others, conclude that nephritis, if it ever occurs as a complication of measles, is exceedingly rare in this connection. Holt[11] has never seen a severe degree of nephritis associated with measles either clinically or at autopsy.

On the other hand malarial fever as an important factor in the production of nephritis has been recognized for a long time. The statistics at the Johns Hopkins Hospital, compiled by Thayer, and published in a recent monograph "On Nephritis of Malarial Origin," show that in 758 cases of malarial fever

treated in the wards, there were 21 instances of acute nephritis; of this number 11 recovered, 4 died, and in 6 the result was unknown. In four instances Thayer believes the process may have assumed a chronic form. He also states (page 23) that, "Out of 112 instances of acute nephritis observed in the Johns Hopkins Hospital, 21, or 18.7 per cent., were of malarial origin." He does not mention measles as a predisposing cause, although he gives statistics of cases of nephritis resulting from diphtheria, typhoid fever and scarlet fever.

Charcot[13] says that the albuminuria coincident with intermittent fever is at times transitory, augmented during the paroxysm, diminishing or disappearing entirely during the intermission, and ceases to exist the moment the fever is cured, or a short time after recovery . . . . . but that at other times the albuminuria persists a long time after the cessation of the paroxysms and takes on decidedly the chronic form.

Hertz[14] in speaking of albuminuria during malarial fever says "More frequently albumin is to be found after long-continued attacks of intermittent fever, or while a person is laboring under the malarial cachexia, and is then constant and quite abundant, depending upon the existence of an enlarged kidney or an amyloid degeneration of the renal vessels."

Rosenstein states that the dropsy and ascites accompanying nephritis of malarial origin attain a higher grade than in nephritis from any other cause.

Bartels[15] claims that next to chronic suppuration "Marsh Miasm" is the most frequent cause of chronic parenchymatous nephritis. He also thinks it may produce this condition without having been attended necessarily by paroxysms of any degree of intensity.

Tirard[16] holds rather uncertain views on this subject, stating that the influence of malaria as an etiological factor in chronic nephritis is open to considerable doubt. Further on he says "It must be admitted also that observations made in Algiers and Bombay show that in these places the association of chronic Bright's disease with malaria is as marked as it is in colder climates; hence the supposition that malarial nephritis is essentially due to exposure to cold scarcely seems to be tenable."

The pathological changes occurring in the kidneys during this disease have been studied by Bignami,[16] Barker,[17] Bastianelli,[18] Laveran,[19] Kelsch and Kiéner,[20] Rem Picci[21] and others.

Kiéner[22] in 1877, seems to have been the first to have worked up the histology with any degree of method; later in 1881 and 1889,[23] in conjunction with Kelsch, the same author did excellent work in this field. In their former work (pp. 279 and 495) they do not identify any particular form of chronic nephritis as the result of the malarial poison, the tissues reacting in the same way as to any other morbid impression, the process not confining itself to either the connective tissue or the secreting portions of the gland, the picture presented being that of a diffuse nephritis. At first the glomeruli and epithelium suffer most, the connective tissue being affected later. This however they do not claim as a fixed rule.

In their later work (page 276) besides going extensively into the pathological anatomy both microscopically and macroscopically they give at length the clinical aspects of the disease. Their conclusions are to the effect that this form of nephritis may be insidious during the course of a chronic malaria and discovered unexpectedly at the autopsy. At other times eclampsia finally reveals very suddenly a lesion already far advanced. In certain cases the symptoms are those attributable to an acute parenchymatous nephritis with anasarca, sudden, considerable and of rapid development, with scanty high-colored and bloody urine. In other cases the urine is clear, slightly albuminous, containing a few hyaline casts.

The consensus of opinion expressed by the different observers of the acute form seems to be that the pathological changes are not great, there being some pigmentation of the glomeruli with albuminous exudates and casts, the epithelium of the convoluted tubules being more or less swollen and degenerated.

Charcot[24] thought that the pigmentary alteration of the cortical substance might possibly be regarded among the organic causes of the persistent albuminuria.

The history of my case is as follows:

M. B., female. Age 7 years 5 mos. Colored. Complains of swelling of the abdomen.

*Family History.*—Negative.

*Past History.*—Child has never been strong, but has escaped the diseases incident to childhood, with the exception of measles, which she had during April, 1898.

In July or August of 1895, '96 and '97, the child visited Prince George's county, Maryland, and upon each occasion contracted chills and fever; the attacks were cut short and apparently cured by the administration of quinine, the paroxysms occurring each day, the chill and fever being quite marked.

The *present illness* dates back to July, 1898, when patient visited Anne Arundel county, Maryland. She commenced feeling badly while there, but did not have marked malarial paroxysms, only an occasional fever and sweat. On her return to Baltimore, at the end of two weeks, the grandmother noticed that the child's face was much fuller than when she left; in fact she thought the child was looking remarkably well. She attached no significance to the swelling till the abdomen commenced to enlarge; she then took her to one of the hospital dispensaries where a careful abdominal examination was made, but neither the urine nor the blood was examined. She was prescribed for, but the condition gradually grew worse, the abdomen becoming so distended that the patient could no longer be carried to and from the hospital. It was at this time, September 24th, that I first saw the child. I found her intensely weak; she could not turn in bed without assistance; there was no headache; appetite fair; no nose bleed, no herpes; slight cough; no pain in back or limbs; bowels loose since taking medicine prescribed at dispensary.

Physical examination showed marked œdema of the face, genitalia and ankles. Abdomen very much distended, tense, and exhibiting the usual signs of ascites; teeth irregular and notched but no pegging; tibiæ rickety; the heart's action was rapid, 128 per minute, forcible, apex not displaced, no murmurs; slight accentuation of aortic and pulmonic second. Lungs gave crackling râles over both bases with marked puerile breathing everywhere; respiration 46 per minute, thoracic in character, temperature 99° F.

The same evening I did a paracentesis abdominis, removing three quarts of turbid fluid, after which abdominal palpation

showed plainly the edge of the spleen about 5 cm. below the costal margin; the liver was not palpable. Suspecting malarial fever, treatment was deferred until the following morning when an examination of the fresh blood was made. This showed one or more intracellular parasites to nearly every field, the infected cells being decidedly smaller than normal, the organism occupying nearly the whole if not the entire corpuscle, the part remaining being greenish and easily discernible. The parasites were quite refractile, the pigment coarse, the granules not numerous, without motion, collected at the periphery and in many instances at the centre. There were many typical segmenting organisms seen, the number of segments ranging from seven to twelve; also one oval form. There were no hyaline forms noted.

This examination was made about 10 A. M., and when the child was seen, about 5 P. M., her temperature was 104.2°. I was prevented from making any further blood examination for three days, quinine being given in 4-grain doses during the interim. The parasites had then disappeared from the cutaneous circulation with the exception of an occasional atypical contracted form, pigmented leucocytes being quite numerous; a leucocyte in process of surrounding a small extracellular pigmented organism was noted.

The urine was light amber, slightly cloudy, acid, sp. gr. 1010. On boiling, almost a solid precipitate was thrown down; Esbach's albuminometer showed 2.1 per cent. albumin.

Microscopically there were hyaline, fine and coarsely granular, also epithelial casts, a great deal of detritus, no red cells, a few leucocytes and epithelial cells.

Fleischl's hæmoglobinometer showed 35 per ct. hæmoglobin.

Upon questioning members of the family further, a history of fever on every fourth day was easily obtained. The absence of chills and the fact that the child had been feverish only occasionally had not led them to suspect a malarial infection.

The treatment instituted was essentially, quinine, Blaud's pills, and later, Basham's mixture or bitartrate of potash; restricted diet and rather free purging. The child's condition improved steadily, the œdema rapidly disappearing; the hæmoglobin when last taken, October 15th, was 65 per cent. The amount of albumin, however, was always high, never going below $\frac{4}{10}$ per cent.; the specific gravity remaining in the neighborhood of 1010. The total amount of urine in 24 hours could not be estimated owing to constant action of bowels.

From October 15th to March 5th, 1899, I saw nothing of patient. On the latter date I was summoned at 10 A. M. and found the child profoundly comatose, pulse 160; she had had several convulsions during the previous five hours; her condition up till the day before had been considered good by the parents. Morphine, chloral, bromide and chloroform were administered with but little effect upon the convulsions, death occurring at 2.30 P. M. An examination of the blood just previously failed to show parasites.

*Autopsy.*—A partial autopsy only was granted, a member of the family remaining in the room. Notes taken just after are as follows:

3.30 P. M. Rigor mortis quite marked. Poorly nourished. Small for age. Rickety. Slight œdema of face and ankles. Abdomen distended, apparently by gas.

Abdominal incision showed marked agglutination of intestines, so much so that in getting back to the kidneys the gut was torn in several places. Edge of liver was not below costal margin; spleen extended about 2 cm. below costal margin; surface rather granular.

*Kidneys* slightly larger than normal, soft, capsule not adherent, surface rather granular, of a pinkish grey color, studded here and there with dots suggestive of fat. On section these same yellowish dots are noted. Cortex somewhat translucent. Striation not at all well marked. Glomeruli indistinct.

Dr. MacCallum who hardened and prepared the sections gives the following report:

Microscopically the kidney presents the picture of a chronic diffuse nephritis of the interstitial type. The glomeruli are extensively obliterated by an ingrowth of connective tissue along the vessels or by a thickening of the capsule. In the section a few are relatively normal, and in nearly all the capsular epithelium is fairly well preserved.

The connective tissue growth is quite diffuse, and the urinary tubules are generally compressed and atrophied. The well-known appearance of dilatation of the tubules in certain areas with flattening of their lining epithelium is present. Such dilated tubules contain masses of granular, colloid or hyaline material mixed with a few leucocytes and desquamated epithelial cells.

The tubules in general show flattening of the epithelium and evidences of degeneration in the epithelial cells. Many are desquamated into the tubules which in places contain a considerable number of polymorphonuclear leucocytes. Fatty degeneration of the cells is not, however, so extensive as one might expect. There seems to be a good deal of fat in the interstitial connective-tissue cells.

The blood-vessels show an extensive endarteritis.

## CONCLUSIONS.

The conclusions to be drawn from this and other cases already on record, especially Thayer's and those of Kelsch and Kiéner, are:

1st. Certainly in some localities malarial fever should be given a prominent position in the etiology of chronic as well as of acute nephritis.

2d. In all cases of malarial fever the urine should be closely watched.

3d. A blood examination should be made in all cases of nephritis occurring in those who have visited or lived in a malarial district, as it often happens that the severe grade of nephritis resulting may mask entirely the clinical picture of malarial fever.

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# A CASE IN WHICH THE BACILLUS AEROGENES CAPSULATUS WAS REPEATEDLY ISOLATED FROM THE CIRCULATION DURING LIFE.

By N. B. Gwyn, M. B., *Assistant Resident Physician, The Johns Hopkins Hospital.*

The generalized distribution of the bacillus aerogenes capsulatus throughout the body, as seen at autopsy, is usually ascribed to a pre-agonal dissemination from a local lesion or other source, and the recognition of the condition has so far been post mortem; the case of Graham, Stewart and Baldwin shows that the organism invading the general circulation may produce characteristic lesions in the tissues several hours before death; in this instance there had occurred an abortion and subsequent infection of the uterus, from which point the general infection proceeded. It is possible that in the living tissues of a subject presenting no local lesion, and whose resistance to infection has not been completely lost, the gas-producing and other functions of an organism may be more or less inhibited and the nature of the infection not become evident. The following case was probably influenced by these conditions, for although the B. aerogenes capsulatus was repeatedly demonstrated during life, none of the characteristic evidences of its presence as seen post mortem were to be made out.

The case, diagnosed as chorea insaniens, gave this history:

Alice B., white, aged 18, school-girl. Admitted May 13, 1899, complaining of St. Vitus's dance; family history, negative; had most of childhood's illnesses, and when 9 years old had mild chorea, from which she completely recovered without subsequent heart or joint symptoms.

Two weeks before admission she had been suffering from insomnia, extreme restlessness and nervousness; a few days later she was said to have been in a condition of severe nervous prostration and was sent home from school. On the way home she suffered from delusions of persecutions, imagining that the passengers would injure her. She showed great incoördination in her gait, reeling from side to side, tossing head and arms about and contorting her face. Her speech was slow, but intelligible. She grew rapidly worse, and by May 12 apparently every voluntary muscle of the trunk, face and limbs was affected, she being unable to talk or to feed herself. On admission she was unable to walk, was unintelligible in talk and quite out of her mind. There were ceaseless involuntary purposeless movements of muscles of face, limbs and trunk, the patient tossing and throwing arms and legs about, muttering and gibbering. There were no joint symptoms; no complaint of pain anywhere; no subcutaneous fibroid nodules; some erythema of elbows and knees from constant friction. Her pulse was regular, rapid, from 100–120. At apex of heart a slight thrill with systole was to be felt. On auscultation merely a booming, first sound, an accentuated pulmonic second sound and a soft systolic murmur over the pulmonary area were heard. There was no pericardial friction.

Her respiration was irregular, partly owing to irregular contractions of abdominal wall; lungs clear; knee-jerks exaggerated; no ankle clonus; plantar reflex present.

Patient improved for first few days after entry; facial movements became decidedly less and her mental condition clearer; the movements of trunk and limbs persisted. During this time her daily temperature had been ranging from 99° to 100° F., the nightly record being often higher, but in order not to interrupt the effects of sedatives was not regularly recorded. Stools and urine were voided involuntarily; in the latter a trace of albumen and a few casts were to be found.

After a few days of apparent improvement her symptoms became exaggerated; the temperature rose to 101.5°–101.7° on May 25 and 27; her pulse became more rapid and weaker. By May 28 her temperature was ranging between 103°–104° F. Her mouth and tongue were dry and fissured, the movements much more marked. Patient began to show signs of extreme exhaustion from ceaseless rolling and tossing. On June 3 she passed into a semi-comatose condition, remaining so till death, on June 6, on which date her temperature reached 106.5°.

A few hours before her death, a large, painful swelling of the right parotid was observed. There was no redness of the overlying skin, no fluctuation and no emphysema. No subcutaneous emphysema was to be felt over the body before or at death; after eight hours in ice-chest there were no alterations to be observed. Unfortunately, no autopsy was obtained.

The rapidly fatal course of this case and the concurrent symptoms suggested at once the presence of an infective agent, and cultures were repeatedly taken to determine its presence; the long-considered connection between rheumatism and chorea induced us to make use of the methods employed in the demonstration of the bacillus of Achalme, described recently by Achalme, Thiroloix and Savchenko in cases of rheumatic fever.

On May 16, 22, 24 and 27, and June 6 cultures were taken

from a vein of the fold of the elbow, 30–50 cc. of blood being extracted and distributed in different media.

*Cultures of May* 16. Aerobic cultures in bouillon and on agar plates and anaerobic in milk and bouillon mixture remained sterile. The cultures of May 22, 24 and 27 were made anaerobically in mixtures of milk and bouillon as recommended by the above observers, tubes of the same lot of media, and cultures from other patients in the same media being employed as controls; to further guard against error, an examination of the fresh blood for organisms was systematically pursued, and on two occasions several distinct bacilli resembling, morphologically, the bacillus to be described could be demonstrated.

All control tubes remained persistently sterile. Pure cultures of a large, non-motile bacillus were obtained from the patient on May 22 and 24, but a failure in obtaining anaerobic condition in the Buchner jar probably interfered with the development of bacilli on May 27. Although the sterility of the control tubes, the presence on two occasions of the same organism and its demonstration in the fresh blood were quite convincing, it may be objected that cultures in fluid media give chances of accidental contamination, and further that no idea of the number of organisms present is obtained. On these grounds, subsequent cultures on June 6 were controlled by the plate method.

As a rule, 5–10 cc. of blood were placed in each tube or plate. After 12–18 hours in Buchner jar at 37°, the inoculated tubes of milk and bouillon showed evidences of a very vigorous bacterial development: on the surface, a pinkish, fissured, firm, retracted clot: clinging to the sides of the tube clots also fissured, and containing gas bubbles, which, rising continually to the surface, formed there a frothy layer. The fluid in the tube had assumed a port-wine color, becoming black on exposure to air. The clot of blood was completely disintegrated, and an aromatic cheesy odor could be detected.

On glucose agar plates after 12–18 hours, 12 small, irregular colonies were visible, which after 48 hours were 1–2 mm. in diameter, gray-brown, with irregular margins, occasionally showing a central dot. An occasional gas bubble was to be seen about some. Numerous colonies of streptococci were also present at the last culture inoculation.

Microscopically, both in fluid and solid media the growth was found to be a large non-motile bacillus 8–10 $\mu$ in length, about 2 $\mu$ in width, very regular in size, with rounded ends, occurring singly or joined in pairs, often at an obtuse angle; rarely were more than 3–4 organisms seen in chains: an appearance as of a capsule was to be seen, which was subsequently demonstrated in experiments. The bacillus stained well by Gram; aerobic growth on the ordinary media did not occur, development taking place only anaerobically or in hydrogen. On agar slants small separate and fused gray-white colonies with somewhat irregular dentate margins were to be seen, an occasional gas bubble developing at bottom of tube.

Glucose agar was regularly broken up, and segments of the media were forced up the tube by the pressure of gas, some fluid appearing on top and in the spaces formed below.

In litmus milk and bouillon, gas formation was shown by the presence of numerous frothy bubbles on surface; in the former, in 18–24 hours, were to be seen fissured and retracted clots in a whey-like fluid, the clots, at first white from decolorization by hydrogen, becoming pink on exposure to air, thus indicating an acid reaction. The bouillon showed general cloudiness with a stringy, yellowish precipitate. Potato gave a scarcely visible film, often with gas formation in fluid below. Gelatin allowed a slow growth with production of gas bubbles and a general softening of the media; no complete liquefaction.

On blood serum (Loeffler) small isolated growths or a film of fused colonies, gray-white in color, developed. An odor of stale glue was noticeable, especially from the growth on solid media. A most abundant growth was always to be obtained in mixtures of milk, bouillon and serous fluid or blood. Under these conditions it could be repeatedly shown that development in presence of oxygen was possible. A standard culture of bacillus aerogenes capsulatus lent me by Dr. Harris responded to the same test. Further aerobic development in transplants on other media from these tubes has so far not been obtained.

Greater regularity of size of the organisms was observed in the young cultures on agar and blood serum; in fluid media short forms and chains appeared, the latter after several days' growth extending over several fields of the microscope; interesting involution forms were often to be seen on surface growths, irregularly staining, dentated, swollen or club-shaped bacilli.

Spores, usually centrally situated, oval, ½–¾ length of containing bacillus, were found on blood serum inoculated from a several days' old milk-tube; occasional end spores were also demonstrated; little swelling of the body of the bacillus was caused by their presence.

Continued transplantation of the organism tended to diminish slightly its size and regularity, smaller diplo-bacillus forms appearing in large numbers; occasionally in media to which blood or serous fluid had been added distinct capsules were to be demonstrated. Experimental inoculations proved that rabbits were insusceptible to intravenous injections of as much as 5–10 cc. of actively-growing culture. Killing the animal 3–5 minutes after the injection and keeping the body at room temperature showed enormous gas development in 4–8 hours. The subcutaneous emphysema, the condition of the liver and other organs, the presence of gas in the heart and vessels, serous cavities and tissues as described by Welch, Nuttall, and Flexner being accurately reproduced.

A slight detonation accompanied the ignition of the gas, which burnt with pale blue flame. Organisms in abundance showing distinct capsules could be obtained in pure cultures from the blood and tissues.

Guinea-pigs were killed in from 36–48 hours after subcutaneous injection. At site of inoculation characteristic lesions were produced, extensive œdematous infiltration of tissues with exudation of bloody serous fluid; in one animal the pericardium was found filled with fluid, evidently an extension of the œdematous process. Numerous bacilli, fibrin flakes and cellular elements containing organisms were present in the exudate; in most inoculations slight gas formation evidenced by emphysematous crackling was noted; in others it was perhaps too slight to be observed; necrosis and rupture of overlying skin were frequently seen.

In pigeons death ensued in shorter time, 24–36 hours. At site of inoculation some slight emphysema could be felt, which, however, might have been post mortem; œdema and sero-sanguinolent exudation with brownish-red discoloration and softening of the muscles were produced. Bacilli in numbers were present in the lesions. Depending upon the time elapsing before autopsy, greater or less numbers of bacilli could be detected in the blood and organs of the guinea-pigs and pigeons.

This resumé of cultural and experimental reactions seems sufficient to show that the organism is identical with the bacillus aerogenes capsulatus of Welch and Nuttall. The cultures obtained on three occasions corresponded accurately, and illustrate the possibility of a long continued infection by this organism, the first positive result being 13 days before death.

The gas-forming property of the bacillus, when in the circulation, may apparently remain in abeyance during the life of the infected individual; the duration of the infection, the seeming abundance of the infecting agent as evidenced by their demonstration in the fresh blood, and the fact that a general streptococcus invasion helped to produce the fatal ending, indicate but a limited degree of virulence on the part of the organism.

It is not assumed that the infection with the bacillus aerogenes capsulatus bears any etiological relation to chorea insaniens, the affection diagnosed in this case, but the bacterial association is of interest in connection with the acute infectious character this disease often presents.

According to Dr. Welch, to whom I am indebted for valuable suggestions, this is the only instance in which the bacillus aerogenes capsulatus has been demonstrated in the circulation during life; whether present as a primary or secondary infective agent is yet to be decided.

# PROCEEDINGS OF SOCIETIES.

## THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

*Monday, March 6, 1899.*

**Remarks upon a Case of Jejunal Fistula.**—Dr. Cushing.

Surgical No. 8025. The patient, Lawrence L., from North Carolina, aged 28, entered Dr. Halsted's service on the 17th of August, 1898, with the history of having received ten years previously a razor cut across the abdomen which had completely severed the intestine in one place and had opened it in two others.

As a result of this injury from which he had made a marvelous recovery, an intestinal fistula, which was practically complete and which had resisted a subsequent operative attempt at closure, had persisted in the abdominal wall. On several occasions he had nearly starved to death from periods of inability to assimilate sufficient nourishment from the ingesta before it was lost through this accidental enterostomy wound.

His appearance on admission was most extraordinary. He was a man of large frame, emaciated to a degree and weighing only 93 pounds. His abdomen and thighs were covered with an acute brilliant dermatitis, which extended from the costal margins almost to his knees resultant to the irritating, continuous discharge from the fistula, which was situated in the median line below the umbilicus. To the right of this in the scar which extended almost across the whole abdomen there protruded a large ventral hernia (cf. photograph) through a transverse separation of the parietes about six centimetres in width.

The coils of intestine in this hernia showed a more or less constant visible peristalsis, and from the fistula, through which a rosette of mucous membrane usually protruded, issued in jets an acid, irritating and frequently bile-stained fluid. The skin everywhere in the vicinity was raw and thickened and so tender it could not be touched. The patient's mental condition, possibly as a result of his chronic starvation, was unbalanced and he had several epileptiform convulsions during his first days in the hospital, and the history mentions the occurrence of similar attacks during the past few years.

He was put in a continuous bath and was fed with nutrient enemata. Attempts to feed through the fistula were unsuccessful. The condition of the skin under water cleared up rapidly and he began to gain in weight under the rectal feeding.

Some months later he was operated upon; the fistula was closed by a resection of the bowel and end-to-end suture over a Halsted inflated rubber cylinder. The adherent coils of intestine were freed from the hernia sac with difficulty, necessitating another partial resection at one place. The abdominal wall was closed without drainage after excision of that part of the parietes involved in the hernia.

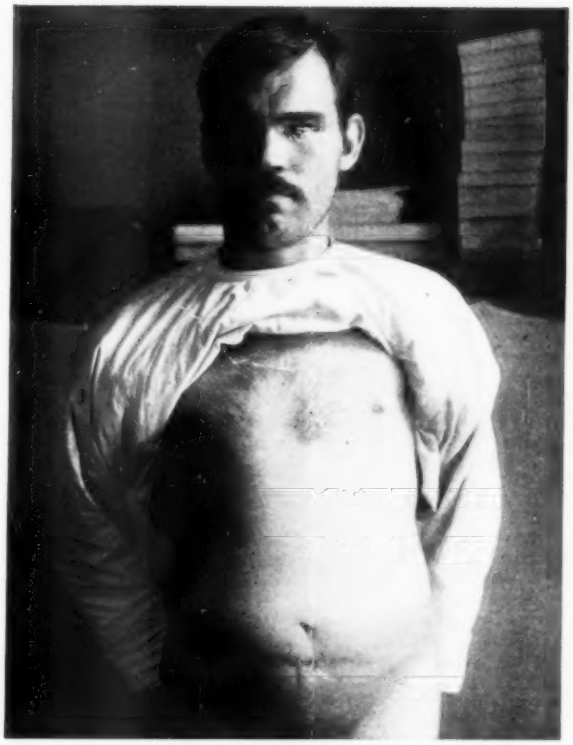
His convalescence was uninterrupted. His weight, 180 pounds to-day, has almost doubled itself since the operation. He gained eleven pounds in one week shortly after the operation.

The case presented many opportunities for physiological study, some of the results of which will be briefly mentioned here.

The *situation of the fistula* was evidently high up in the alimentary canal as was evidenced by the irritation produced upon the skin by the discharges.

It has been a common observation that the degree of dermatitis surrounding an intestinal fistula becomes more pronounced as the situation of the opening approaches the duodenum. The usual colostomy made in the large bowel causes no cutaneous irritation. It seems not unlikely that the pancreatic juice is chiefly responsible for this condition, as no fistulæ are so intensely irritating to the skin as those produced by opening and draining pancreatic cysts which have retained some communication with the secreting gland. In two other cases of high fistula now present in the wards, it has been necessary to place the patients in a continuous bath to control this acute eroding dermatitis. One was the result of a temporary fistula at the site of suture following a pylorectomy for carcinoma; the other was resultant to the establishment of a jejunostomy for post-operative obstruction. Biliary fistulæ are unirritating. Gastric fistulæ are commonly not followed by cutaneous inflammation.

December, 1898, weight 93 lbs.



February, 1899, weight 178½ lbs.

*Surgical No.* 8025. *Case of Jejunal Fistula and Ventral Hernia.*

A method of determining the *exact distance of the fistula from the stomach* was suggested by the accidental discovery that oysters were discharged from the opening a short time after ingestion, practically unchanged. A piece of ligature silk was sewed through one of these before it was swallowed and three hours later the oyster appeared at the fistula. On careful measurement it was found that 3 feet 11 inches of string reached from the patient's teeth to the fistula. Peristaltic action was so strong and tugged at the string so vigorously after the oyster had been expelled that the patient had tied the buccal end of it about a lead pencil, which he was wearing between his teeth like a bit to prevent the string's disappearance. This measurement showed the fistula to be high in the jejunum, possibly one foot below the duodenum.

*Physical examination* of the stomach showed that there was no dilatation despite the extraordinary amounts of food, solid and liquid, with which the patient was accustomed to gorge himself at frequent intervals. Naturally a condition of chronic gastritis was present and the stomach contents after test meals showed great variability on chemical examinations. The reaction was always acid, sometimes due to free HCl, sometimes when this was absent, to fatty acids. This lack of constancy in the analysis of the gastric secretions unfortunately led to some variability in the results of many of our observations.

The *propulsive power* of the stomach and intestine above the fistula was very great. A glass of milk given on an empty stomach on one occasion began to appear, acid in reaction and finely coagulated, at the fistula in one minute and had been entirely recovered in four minutes. This rapid emptying of the stomach seemed most extraordinary. The patient had learned to prevent this immediate loss of food by swallowing large unmasticated pieces of meat and vegetables so that he would occasionally succeed in obstructing the pylorus and apparently at times the fistula itself, thus allowing of some absorption by the bowel above or possibly of some passage by the fistula. When the stomach was empty, peristalsis of the proximal bowel, seen through the thin parietes covering the hernia, was especially active and associated with "gnawing cramps" and the mucous membrane would protrude from the fistula to such an extent that on one occasion it became nearly strangulated when food had been withheld for 12 hours. (Cf. Photograph I.)

This motive activity was further shown by the fact that cold beverages would appear at the fistula before they had been warmed to the body temperature. A glass of ice water would reduce the temperature at the fistula a full degree while it was being discharged, and at such times the coils of intestine adherent in the hernial sac felt perceptibly cold to the hand.

Attempts to determine the *absorptive power* of the stomach were unsatisfactory. The fistula was too tender to allow the wearing of any apparatus to collect the discharge. Under ordinary circumstances when the stomach was empty there seemed to be no diminution whatever in the fluids collected from the quantity taken into the stomach. Whether there was some absorption when the bowel or fistula was blocked with food could not be certified.

The *reaction* at the fistula despite its proximity to the pancreatic ducts was quite uniformly acid, increasing in degree during digestion. It was due largely to the presence of fatty acid.

Some observations of great interest were made with Dr. Clopton on the *bacteriology* of the contents of the bowel under various conditions. These will be published in full in a forthcoming paper on the flora of this part of the intestinal tract. The great variation of the gastric acidity, chiefly in HCl, unfortunately made these observations at times somewhat uncertain. During active digestion on a mixed diet the flora of the discharge showed great diversity of organisms. It was found that several varieties of pathogenic bacteria taken into the mouth in inoculated milk could be recovered readily and grown at the fistula. We also succeeded in demonstrating that the ingestion of a sterilized diet, the mouth meanwhile being rendered as clean as possible by frequent antiseptic washes, was followed by a pronounced diminution in the number of colonies on plates inoculated from the lumen of the proximal bowel. For forty-eight hours before the operation every precaution was taken to prevent the entrance of micro-organisms through the mouth, and, at the time of operation, cultures taken from that part of the bowel above the fistula, where a partial resection was rendered necessary, remained sterile, and no organisms could be demonstrated on stained preparations from the mucosa. Resection and "end-to-end" suture followed by closure of the parietes without drainage, under such circumstances, is attended with little risk.

I regard this as an all-important procedure, when time permits, in the preparation of a patient for a laparotomy during which the bowel is likely to be opened or when a resection and suture is premeditated. The results of observations in this direction during the past year will be published.

**Treatment of Acute Otitis Media following Influenza.**—DR. THEOBALD.

I wish, to-night, to speak more especially of the abortive treatment of these cases when one can see them in the earliest stage.

There have been, as you probably know, an exceptional number of serious ear troubles following the influenza or grippe. The statistics bearing upon this subject that Dr. Bacon gives in his recently published treatise upon the ear are interesting. He says that a few years ago 12 to 20 cases of mastoid disease were about the average met with in the course of a year in the New York Eye and Ear Infirmary, while in 1897 there were 161 mastoid operations. He attributes this great increase to the prevalence of influenza.

The most serious involvements are those in which the brain is affected. This may happen in several ways. Epidural abscess is one of the more common forms, and purulent meningitis is another. Abscess of the brain substance itself or thrombosis of the lateral or sigmoid sinus are other ways in which the brain may be involved.

The modes of infection of the middle ear may be referred to in passing. The most common way is through the Eustachian tube. Nature has provided a means for lessening the likelihood of this happening, the ciliated epithelium of the Eustachian tube acting in such a way as to hinder the entrance of bacteria

from the nasal cavity into the middle ear, but it is only partially successful. Another route of infection is through a perforation in the tympanic membrane. The infection may occur also through the blood-vessels or the lymphatics.

Various micro-organisms have been found in suppurative middle ear inflammations. The staphylococcus aureus and albus, the streptococcus pyogenes and the pneumococcus are among the most common, the two first-named being found especially in the milder cases. The micro-organism that is supposed to be the cause of influenza is occasionally found, but is usually accompanied by other organisms. My own experience is, that the purulent infection occurs very frequently, only after perforation of the tympanic membrane. This is not always so, for often when the tympanic membrane is incised pus escapes; but not infrequently the discharge is not purulent but sero-mucoid, tinged with blood, and does not until later become purulent. It is a very difficult matter, even with antiseptic precautions, to prevent infection after a perforation has occurred or an incision has been made through the tympanic membrane, for one cannot sterilize the skin of the external auditory canal as thoroughly as the skin upon other parts of the body may be sterilized.

Every one is familiar with the symptoms of inflammation of the middle ear. Pain is the most prominent symptom, and deafness occurs, but the pain is so great as to prevent attention being called to the latter. Tinnitus aurium is usually present. The temperature, in children especially, is apt to run high. Even in uncomplicated cases in children it may reach 105°. In adults we are not apt to have so high a temperature unless there are serious complications.

In the beginning of the attack, if we inspect the ear with the mirror and speculum, we will see a hyperæmia of the upper part of the membrane, especially of Schrapnell's membrane, and running down the handle of the malleus will, perhaps, note a line of congested vessels. A little later, the whole membrane becomes red and loses its normal appearance. If the attack runs a little longer we shall usually find evidences of fluid in the tympanic cavity, causing bulging of the membrane, usually of the posterior and lower quadrant, but sometimes of the membrana flaccida.

What I want to speak of more particularly is the early treatment of these middle ear inflammations, especially of those cases following the grippe. I believe, in the large majority of instances, if we can see these cases early, that is, within a few hours of the onset of the pain, we can cut short the attack. I think it is greatly to be desired that this should be accomplished, for if the inflammation is not controlled promptly it is extremely difficult to prevent suppuration. Even when this occurs, most of these cases, it is true, do well; but we never know when serious complications may supervene.

I have recently met with the most rapid death following ear disease that I have ever encountered. The patient had had influenza, had been out and exposed to cold, and was taken on Friday with ear-ache. She suffered severe pain Friday night and Saturday and was given morphia liberally to relieve the pain. On Sunday she showed signs of nervousness and irritability, and when I saw her, for the first time, on Tuesday evening she was delirious, had a temperature of 105°, and a very rapid pulse, and a look into the eyes satisfied me that there was commencing optic neuritis.

There was no reason to suppose, in this case, that the mastoid process was involved, but it was evident that there had been a direct extension to the brain from the tympanum, and there was no doubt of the existence of a meningitis. An extensive operation upon the brain suggested itself as a possible means of relief and, at my suggestion, Dr. Finney saw the case, but he thought the condition of the patient was such that no operation was advisable, and she died on the following morning. This is an extreme instance of how rapidly ear disease may induce fatal brain complications. If, then, we can abort these cases, in which such a result is a possibility, it is most important to make the attempt and make it early. The plan of treatment which I recommended years ago, and for which I have been given considerable credit, although I do not deserve it, as the suggestion was not original with me, is the using in the ear of a solution of atropia, to which I have added more recently cocaine. I prescribe either a watery solution of atropiæ sulphate and cocaine muriate, or a solution of the alkaloids of atropia and cocaine in oil of sweet almonds. In either case the strength of the solution is half a grain of atropia and one grain of cocaine to the drachm. The advantage of the oily solution is that it remains in contact with the tympanic membrane for a longer time and so favors freer absorption, and further, if there is a perforation of the membrane present it is not so likely to find its way through the Eustachian tube to the throat and produce constitutional effects. When the solution is to be put into the ear the patient should lie down with the affected ear up, and should be kept in this position for at least ten minutes, so that the solution may remain upon the tympanic membrane. A little cotton can then be put in the ear and the head raised.

Eight drops of the solution, warmed (5 or 6 drops in the case of children), are used at a time. This means about 1-15 grain of atropia; but the absorption is very imperfect and there is no danger of constitutional effects from the application, unless a perforation of the membrane exists. Where this is the case, however, one should be a little cautious, and I always speak of the possibility of constitutional effects, and advise accordingly. The instillations may be repeated 3 or 4 times a day as long as pain is present. I have seen occasionally slight evidences of the systemic action of atropia from this plan of treatment, but never anything alarming. In addition to this local treatment I give small doses of calomel every hour or half hour until the bowels are freely moved, and if the effect of the calomel in this respect is slight I prescribe a saline cathartic.

The result of this plan of treatment, if only one sees the case in its incipiency, is usually extremely satisfactory. The pain is often relieved within a few hours and the inflammatory process controlled so effectually that in the majority of cases an incision of the membrane or a spontaneous perforation is avoided.

After the acute symptoms have subsided, the tinnitus and deafness which are apt to remain are benefited by liberal doses of muriate of ammonia—ten grains, three or four times a day. If the pain is not controlled by the cocaine and atropia instil-

lations, antikamnia or phenacetine may be administered, or, if necessary, morphia. It is not safe, of course, to wait indefinitely for the effects of this treatment; but my experience with it has been so favorable that I am sure I wait longer than many do before incising the tympanic membrane. If it is evident that the tympanum is distended with fluid a free incision should be made, preferably through the posterior portion of the membrane.

One does not make a small puncture, as was formerly advised, but a free incision, beginning it well up and carrying it down parallel with, and close to, the posterior margin of the membrane. After this the ear should be syringed with a saturated solution of boracic acid two or three times a day, and if this does not control the suppuration a solution of bichloride of mercury, 1 to 8000 to 1 to 4000, may be employed instead.

The effect upon the hearing in these cases is not usually disastrous. In the mastoid cases the impairment is often pronounced and permanent. In the milder suppurative cases, however, we expect a complete restoration of the hearing.

DR. REIK.—I would like to add a few words to what Dr. Theobald has said concerning the treatment of these cases. As Dr. Theobald has already said, there has been a larger number of cases of otitis media accompanying or following the recent epidemic of grippe than has occurred in the past. I fully agree with the method of treatment he has outlined except that I am, perhaps, in favor of incising the drum membrane at an earlier stage.

Wishing, however, to avoid an operation wherever possible, I have frequently made use of local blood-letting in addition to the treatment described by Dr. Theobald. I apply one or two leeches over the mastoid region and allow the bleeding to continue for some time after their removal. It is remarkable in many cases to note the great relief that follows almost immediately upon their application. The pain ceases to such an extent that the patient soon falls asleep and the inflammation is retarded.

DR. THEOBALD.—There can be no doubt of the value of local blood-letting in these cases.

DR. FINNEY.—I saw the case Dr. Theobald referred to, a few hours after Dr. Theobald saw her. She was then comatose, with a pulse that could hardly be counted, a temperature of 105 to 106 degrees, very high, and utterly beyond operative aid.

There was at that time no evidence that would aid in the localization of the trouble. There had been no paralysis, no muscular contractions; the pupils were of the same size and there was no evidence of any trouble or any other evidence that I could detect by examination or the history of the case, that would aid in localizing the process, and even had we gotten any idea of the location of the trouble, I thought at that time, there would have been no use in operative interference.

I saw one other case, just a day or two before this one, that was similar in many respects, only of more happy termination. Also a young woman, sick for two or three days, had had grippe and recovered from that apparently, and a week later complained of headache which lasted for some time, only very intense she said, and always referred to right ear. After a few days she noticed a certain amount of discharge on the pillow in the morning, supposed to be from the ear, although the physician who saw her said he could find no discharge from the ear, nor was there any discharge from either ear that I could detect at the time I saw her. The drum upon that side was ruptured, she was stupid, dull, very different from the usual vivacious temperament. Could be roused enough to answer questions intelligently, but it required considerable effort to rouse her. Upon pressure over the mastoid she evinced some pain. No swelling or other evidence of mastoid trouble.

We thought it best to open the mastoid and did so and found no evidence of trouble so far as I could detect. I continued the opening in the bone until I exposed the lateral sinus and punctured that. It bled very vigorously and I came to the conclusion that the lateral sinus was not at any rate thromboosed. I drained the wound, and the patient from that time made a rapid recovery and is now entirely well.

**Some Objections to the Neurone Theory.**—DR. PATON.

The investigations of Apáthy, Bethe and Nissl have shown that the ganglion cells in the spinal cord and brain contain a specific fibrillar substance essentially different from the protoplasm of the cell body and its processes. This substance can be stained by several different methods. Little is known of its origin. It may be shown to be an integral part of the ganglion cell or it may develop from other cells in the nervous system, or it has been suggested that it may be the product of both kinds of cells.

Until it has been determined histogenetically that the fibrillary substance is a part of the ganglion cell it is an assumption to speak of these cells as units or individuals. The picture of the ganglion cell, obtained by the use of Nissl's methylene-blue method, is the negative of that given by Bethe's new stain. The achromatic tracts in the first correspond to the colored tracts or fibrils in the second specimen. Nissl believes that the fibrillary substance is present, not only in the cells, but exists in large masses in the intercellular substance and is one of the important constituents of the grey substance.

In the main the fibrils follow the distribution of the dendrites and axons. The life of the fibrils undoubtedly depends upon the preservation of the myelin sheath. There is nothing revolutionary in the new discoveries in relation to the studies of the degeneration of nerves. Little has been done in studying degenerations. Bethe has cut peripheral nerves and found that the fibrils degenerated, and that in a short time there is nothing left but granular masses. There is a great deal of interesting work to be done on this subject. Nissl emphasizes the importance of the nerve cell as a nutritive centre. If later the fibrils are proved to develop in the nerve cell, and not from other cells, it will no longer be an assumption to speak of the nerve cell as a unit.

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